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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A01N 43/20 — A1

(11) International Publication Number: **WO 99/65307**

(43) International Publication Date: 23 December 1999 (23.12.99)

(21) International Application Number: PCT/US98/06221

(22) International Filing Date: 30 March 1998 (30.03.98)

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF AIDS-ASSOCIATED KAPOSI'S SARCOMA

(57) Abstract

The present invention comprises methods and compositions for treating a human with AIDS-associated Kaposi's sarcoma. More specifically, the method comprises administration of a taxane composition over a 3 hour infusion schedule. Importantly, the compositions and methods of administration allows for reduction of side effects and reduces the symptoms of Kaposi's sarcoma.

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METHODS AND COMPOSITIONS FOR TREATMENT OF AIDS-ASSOCIATED KAPOSI'S SARCOMA

Cross-Reference to Related Applications

This application claims priority to U.S. Provisional Application No. 60/041,651, filed March 27, 1997.

Technical Field

The present invention relates to methods and compositions for treating AIDS-associated Kaposi's sarcoma in humans. More particularly, the present invention relates to methods for treating AIDS-associated Kaposi's sarcoma using a taxane composition.

Background of the Invention

Kaposi's sarcoma (KS) was initially described in 1872 and, as originally described, is a rare tumor with an indolent clinical course occurring mainly in elderly males of Mediterranean or Ashkenazi Jewish descent. This form of KS is characterized by lower extremity skin nodules caused by blood vessel proliferation. The usually benign skin lesions in these patients rarely caused any problems or required any treatment.

With the advent of the AIDS era, a virulent form of KS has been expressed in individuals made immunodeficient by HIV (Human Immunodeficiency Virus). AIDS (Acquired Immunodeficiency Syndrome) and HIV infection cause worldwide healthcare problems, including a worldwide increase in the incidence of Kaposi's sarcoma. In the United States in 1996, AIDS-associated Kaposi's sarcoma occurred in approximately 17% of gay men with AIDS and 1-5% of others infected with HIV. As the most common AIDS-related tumor, the treatment of KS has become an important facet of the treatment of AIDS. In association with AIDS (Acquired Immunodeficiency Syndrome), KS commonly presents as an aggressive widely disseminated neoplasm. The KS neoplasms arise in multiple foci from vascular endothelium or lymphatic tissue in skin, mucosal surfaces, lymph nodes and visceral organs, including liver, spleen, gastrointestinal tract and lung.

In some HIV positive patients, KS is confined to the skin and may not require intensive therapy. In contrast, other patients have an aggressive form of KS where lesions commonly progress from macules to plaques and nodules, which often coalesce and ultimately develop into fungating or ulcerated masses.

At the initial clinical presentation, many patients with AIDS-associated Kaposi's sarcoma present with multiple organ involvement. The most common, and also the most life-threatening, organs involved are the gastrointestinal tract and the lung. Gastrointestinal lesions are frequently associated with enteropathic and hemorrhagic symptoms. Pulmonary involvement may be particularly ominous and is often mistaken for opportunistic infections on clinical grounds.

Krown and colleagues developed a system for uniform staging and evaluation of clinical trial outcomes for AIDS-associated Kaposi's sarcoma patients based on three broad stratification criteria: a) Extent of tumor involvement; b) Immunologic status; c) Systemic illness. See Krown *et al.*,

"Kaposi's sarcoma and the Acquired Immunodeficiency Syndrome: A Proposal for Uniform Evaluation, Response and Staging Criteria." J. Clin. Onc. 7:1201 (1989). They divided patients into good risk or poor risk based on the extent of tumor, the number of CD-4 positive cells, and whether or not associated systemic illness was present. This staging system, slightly modified, has been shown in a retrospective analysis to be predictive of survival.

Cure or long-term complete remission of AIDS-associated Kaposi's sarcoma is unlikely with currently available treatment. Prior to the present invention, the major goal of treatment for AIDS patients with KS was alleviation of symptoms, shrinkage of the tumors to relieve edema, organ compromise or psychological stress, and prevention of disease progression. Such treatments include local therapies that have been useful for palliation of localized cutaneous and mucosal lesions. Local therapies include radiation therapy, laser therapy, and whole lung irradiation. Surgery as a means of controlling KS has been found to be of minimal benefit.

Intra-lesional drug administration utilizing vinblastine, bleomycin, interferon, or TNF (tumor necrosis factor) has induced tumor regression. Other experimental biomodulatory agents have also been used intralesionally. These treatments generally require multiple injections and cause local inflammation that may result in ulceration, pain and secondary infections.

Photodynamic therapies have also been used to treat AIDS-associated Kaposi's sarcoma. Phototherapeutic drugs such as dihematoporphyrin were administered followed by laser treatment. Patients undergoing this therapy have to avoid direct sunlight, bright incandescent light or radiant heat for 30 days after treatment. This inconvenience for the patient and the need for special laser equipment makes this treatment plan unwieldy for most KS patients.

While these local approaches may temporarily alleviate symptoms, AIDS-associated Kaposi's sarcoma usually requires systemic therapy. Such systemic treatment has evolved from early trials of single cytotoxic or antiviral agents to combinations of cytotoxic and antiviral drug therapy. Prior to the present invention, none of the currently available treatments, single or combination administration, have proved to be successful over the long term without significant side effects.

Several cytotoxic agents, including the vinca alkaloids, vincristine, anthracyclines, platinum, and bleomycin have demonstrated anti-tumor activity in up to 40-50% of patients. Combinations of these agents may induce responses in up to 85% of patients and a combination of adriamycin, bleomycin, and vincristine (ABV) induced a complete response in nearly 40% of patients. In a prospectively randomized fashion, Gill *et al.* compared ABV with doxorubicin alone and demonstrated a disease-free survival of nine months with the combination vs. 3.5 months with the single agent. Overall survival was not significantly impacted. See Gill, P.S. *et al.*, "Systemic Treatment of AIDS-related Kaposi's Sarcoma: Results of a Randomized Trial", Am. J. Med. 90:427 (1991).

Recently, taxanes, such as paclitaxel, have been shown to have antitumor activity in a variety of tumors. Paclitaxel is a novel microtubule stabilizing antitumor agent, originally isolated from the stem bark of *Taxus brevifolia,* the western (Pacific) yew tree. Paclitaxel acts by promoting the formation of unusually stable microtubules, and inhibits the normal dynamic reorganization of the microtubule network required for mitosis and cell proliferation. (See Schiff, P. B., *et al.* (1979) Nature 277, 665; Schiff, P. B., *et al.* (1981) Biochemistry 20, 3247). In the presence of paclitaxel, the concentration of tubulin required for polymerization is significantly lowered. Microtubule assembly occurs without GTP and at low temperatures, and the microtubules formed are more stable to depolymerization by dilution, calcium, cold, and

inhibitory drugs. Paclitaxel reversibly binds to polymerized tubulin, and other tubulin-binding drugs will bind to tubulin in the presence of paclitaxel.

A proposed mechanism for paclitaxel is that paclitaxel interacts with the microtubule system of many types of organisms. For example, in mammalian cells a 50 nM paclitaxel concentration usually causes a significant increase in microtubule number, with changes in cell shape and mitotic arrest in actively dividing cells. (Parness, J., *et al.* (1982) Biochem. Biophys. Res. Commun. 105, 1082). These perturbations of microtubule function caused by paclitaxel have a critical impact on the cell because of the role played by microtubules in cell motility, secretion, and cell division.

Other mechanisms of paclitaxel have been recently demonstrated. Paclitaxel induces apoptosis in cells by bcl-2 phosphorylation which is triggered by cRaf-1 activation. See M.V. Blagosklonny *et al.*, (1996),Cancer Research, 56(8):1851-1854. Paclitaxel has also been shown to inhibit angiogenesis, a mechanism that is of particular interest in KS. See Klauber *et al.*, Cancer Research (1997) 57:81-86. The tumors of KS are characterized by aberrant and enhanced proliferation of vascular structures.

Paclitaxel has been studied for its effect in combating growth of various tumors in numerous clinical trials using a variety of doses and administration schedules. Severe allergic reactions have been observed following administration of paclitaxel. However, it has been demonstrated that the incidence and severity of allergic reactions is affected by the rate of paclitaxel infusion and premedication with corticosteroids and antihistamines. (Weiss, R B., *et al.* (1990) J. Clin. Oncol. 8, 1263). Subsequently, paclitaxel has been approved as a second-line treatment of ovarian and breast cancer in the US and other countries. The success rate for tumor treatment with paclitaxel has been shown to be very dependent upon dose and administration regimen.

AIDS-associated Kaposi's sarcoma has previously been successfully treated with paclitaxel. These patients were not undergoing concurrent treatment with viral protease inhibitors. Saville et al, in a phase II study using Taxol® (a Bristol-Meyers Squibb formulation of paclitaxel), at a dose 135 mg/m^2, administered intravenously over a three hours period every 21 days, have demonstrated a response rate of 65% (13/20 patients) in patients with AIDS-associated Kaposi's sarcoma. These thirteen patients had partial response, as defined by the modified Krown's method used. See Saville, *et al.*, "Treatment of HIV-Associated Kaposi's Sarcoma with paclitaxel (Taxol ®)". Lancet 346:26-28, 1995. Each of the five patients with pulmonary involvement responded. Neutropenia was the most frequent dose limiting toxicity. There were also some novel paclitaxel toxicities observed including fevers, rash and eosinophilia.

In another study, Gill *et al.*, in a phase II study of paclitaxel at a dose of 100 mg/m^2, administered over 3 hours every 14 days, for patients with advanced or refractory AIDS-associated Kaposi's sarcoma, reported a 59% (16/27) response rate. The remaining 41% (11/27) of the evaluable patients had stable disease. Improvement in symptomatic lymphedema was noted in 19 of 20 patients. Thirty-seven percent of the patients experienced Grade 3-4 neutropenia. See Gill, P.S., *et al.* submitted to 1995 ASH annual meeting December, 1-5, 1995, and Gill, P.S., *et al.*, Paclitaxel (Taxol) in the Treatment of Relapsed or Refractory Advanced AIDS-related KS, ASCO, May 1996.

Paclitaxel, like other chemotherapy agents, has been shown to create drug resistance in tumor cells. Drug resistance by tumor cells is a common response to chemotherapy agents. Two mechanisms of paclitaxel resistance have been identified *in vitro*. In one cell type, resistance is due to drug efflux, which is the result of increased levels of membrane P-glycoproteins causing increased drug efflux. (Gupta, R. S. (1985) Cancer Treat. Rep. 69, 515). These cells are also resistant to the vinca alkaloids, doxorubicin, and other natural products, and resistance

is reversible with calcium channel blockers such as verapamil (Racker, E., *et al.* (1986) Cancer Treat. Rep. 70, 275). Another mechanism of resistance found in other paclitaxel resistant cells involves mutations in the alpha- or beta-tubulin subunits. (Schibler, M. J., *et al.* (1986) J. Cell Biol. 102, 1522).

An added consideration when treating AIDS-associated Kaposi's sarcoma is the treatment that the patient is undergoing for the underlying HIV infection. Though treatment of HIV infection with AZT (zidovudine) first appeared to be effective, it has been found that many patients cannot tolerate AZT for very long or that AZT had little effect on the progression of their disease. Combinational therapies, including AZT combined with other nucleoside analogs such as ddI or ddC, have been shown to be somewhat effective in overcoming problems associated with AZT administration alone. Combinational therapies have also included the reverse transcriptase inhibitors such as lamivudine, nevirapine, and stavudine.

One of the more recent treatments for AIDS/HIV that shows promise is the administration of viral protease inhibitors to block the replication of the virus itself. An example of such a viral protease inhibitor is Norvir™, a product of Abbott Laboratories, commonly known as ritonavir. Other known protease inhibitors include indinavir, nelfinavir, and saquinavir. Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polypeptide precursor which leads to production of non-infectious immature HIV particles. Like other AIDS therapies, ritonavir-resistant HIV-1 isolates have been found *in vitro*.

At the present time, ritonavir is indicated in combination with nucleoside analogs or as monotherapy for the treatment of HIV-infection when therapy is warranted. The combination of ritonavir with certain other therapeutic agents is contraindicated because ritonavir changes the pharmacokinetics of

many other drugs. Ritonavir is metabolized by cytochrome p450 enzymes and thus it may inhibit the metabolism of other drugs. Therapy with ritonavir is expected to produce a large increase in plasma concentrations of many drugs including bepridil, bupropion, piroxicam, cisapride, quinidine and rifabutin. Use of protease inhibitors with sedatives such as alprazolam, diazepam and zolpidem has the potential for extreme sedation and respiratory distress and thus coadministration is contraindicated. Use of chemotherapeutic agents with protease inhibitors must be monitored closely because of the potential large increase in the plasma concentration-time curve, a measure of drug exposure. Such chemotherapeutic agents include paclitaxel. See package insert for Norvir or other protease inhibitors for a complete list of agents.

Protease inhibitors do not provide a cure for HIV infection and thus the HIV-associated pathologies of AIDS, including KS, will continue to be a significant health concern. With the advent of protease inhibitors for treatment of AIDS, there is new hope for treatment of AIDS and its associated syndromes such as KS. What is needed therefore are new methods and compositions for AIDS-associated Kaposi's sarcoma that can be used in AIDS patients who are undergoing new treatments for the AIDS virus, such as viral protease inhibitors. Particularly what is needed are methods and compositions for patients who have refractory AIDS-associated Kaposi's sarcoma who are undergoing HIV treatment with viral protease inhibitors. Furthermore, prior to the present invention, no one has been able to demonstrate an effective regimen for treatment of patients undergoing antiviral treatment with viral protease inhibitors, who have AIDS-associated Kaposi's sarcoma, that provides long-term cessation of KS tumor growth and alleviation of associated problems of pain or organ involvement.

What is also needed are methods and compositions for treatment of AIDS-associated Kaposi's sarcoma in patients who have undergone liposomal anthracycline therapy that was

unsuccessful. Thus, methods and compositions are needed that are capable of treating AIDS-associated Kaposi's sarcoma that is resistant or refractory, and that are safely and effectively combined with HIV therapeutics such as viral protease inhibitors. Moreover, an infusion treatment regimen that would be efficacious in this treatment would be beneficial. Additionally, methods and compositions that are easily administered are needed. In addition to infusion methods, a simple and efficacious method of treatment would be through the oral route.

Summary of the Invention

In accordance with the present invention, compositions and methods are provided for treating Kaposi's sarcoma (KS) associated with HIV (human immunodeficiency virus) infection or AIDS (Acquired Immunodeficiency Syndrome). In particular, the compositions and methods are effective for persons who are undergoing treatment for HIV infection that includes administration of protease inhibitors. Also, the compositions and methods of the present invention are effective for persons with AIDS-associated Kaposi's sarcoma who have failed liposomal anthracycline treatment for KS. These compositions are easily administered and can be given in dosages that are safe and provide for manageable side effects.

The present invention comprises methods and compositions for treating Kaposi's sarcoma. Such methods and compositions comprise initial induction treatments and long-term maintenance treatments with taxanes such as paclitaxel. Such an initial induction treatment method comprises infusion times of at least approximately 3 hours every two weeks, for approximately ten cycles of treatment. Long term maintenance treatment methods are effective to maintain clinical level tumor response and stabilization of disease. Such long-term schedules may enhance the activity of taxanes, such as paclitaxel. Thus a preferred embodiment of the long term maintenance method of the present invention is to administer a taxane such as paclitaxel as

a 3 hour infusion treatment, every two to four weeks, for more than 10 cycles, in patients with AIDS-associated Kaposi's sarcoma, to effectively treat the KS tumors and to alleviate the symptoms associated with KS.

The present invention also includes KS treatment compositions that comprise paclitaxel for treatment of HIV infected patients who are undergoing treatment for viral infection by administration of viral protease inhibitors or other new treatments that are metabolized by the liver. These patients may or may not have previously been treated unsuccessfully with liposomal anthracycline treatment for KS. Such compositions may be administered to humans with AIDS-associated Kaposi's sarcoma who are also taking viral protease inhibitors at paclitaxel doses of approximately 20 mg/m^2 to 200 mg/m^2, more preferably at doses of 50 mg/m^2 to 150 mg/m^2, most preferably 100 mg/m^2, the dose level being dependent on the efficacy and toxicity of paclitaxel in the patient.

The present invention also includes compositions and methods for treatment of tumors with taxanes. Such compositions and methods may use various administrative routes for treatments of tumors. AIDS-associated Kaposi's sarcoma is a tumor that has been found by the present inventors to be treatable by administration of taxane compositions, and other tumor types are also treatable with the compositions and methods of the present invention.

Accordingly, it is an object of the present invention to provide methods and compositions to treat AIDS-associated Kaposi's sarcoma.

Another object of the present invention is to provide compositions comprising taxanes for the treatment of AIDS-associated Kaposi's sarcoma.

It is yet another object of the present invention to provide methods of treatment of AIDS-associated Kaposi's sarcoma comprising long-term treatment with at least 10 cycles of taxane treatment.

It is another object of the present invention to provide methods of treatment for patients with AIDS-associated Kaposi's sarcoma that have had tumor progression or no remission of disease after treatment with other chemotherapy regimens.

It is yet another object of the present invention to provide a treatment for patients with AIDS-associated Kaposi's sarcoma who were refractory to treatment with liposomal anthracycline treatments.

A further object of the present invention is to provide methods and compositions for treatment of AIDS-associated Kaposi's sarcoma in patients who are also concurrently undergoing treatment for viral infection by administration of viral protease inhibitors.

An object of this invention is to provide methods and compositions for treatment of AIDS-associated Kaposi's sarcoma in patients who are currently undergoing treatment for viral infection by administration of nucleoside or other antiviral compositions.

It is another object of the present invention to provide methods and compositions for paclitaxel administration that reduce or alleviate the symptoms of AIDS-associated Kaposi's sarcoma in persons infected with HIV.

A further object of the present invention is to provide methods and compositions for treatment of AIDS-associated Kaposi's sarcoma in patients who are also concurrently undergoing treatment for viral infection by administration of combination therapy including viral protease inhibitors and nucleoside analogs or reverse transcriptase inhibitors.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and the appended claims.

Detailed Description

The present invention comprises compositions and methods for the treatment of AIDS-associated Kaposi's sarcoma. One embodiment of the present invention is the use of taxanes, such as paclitaxel or taxotere, via long-term schedules of at least 10 cycles, to treat patients with AIDS-associated Kaposi's sarcoma who are also undergoing antiviral treatment, such as viral protease inhibitors. The present invention also comprises shorter-term schedules of patients. The present invention also contemplates compositions and methods for treatment for patients undergoing antiretroviral therapy that has been recognized by governmental agencies such as those recommended by guidelines provided by the Department of Health and Human Services, U.S. Government. The present invention also comprises treatment of patients with AIDS-associated Kaposi's sarcoma who have failed liposomal anthracycline treatments for Kaposi's sarcoma. As used herein, taxane treatment includes treatment with paclitaxel, Taxol® (BMS), and Taxotere®, docetaxel, or combinations of taxanes, and where paclitaxel is used herein, the other taxanes could be substituted therefor.

A known proposed mechanism for paclitaxel is that paclitaxel interacts with the microtubule system of many types of organisms. Other mechanisms of paclitaxel activity include induction of apoptosis in cells by bcl-2 phosphorylation, triggered by cRaf-1 activation and inhibition of angiogenesis. Though not wishing to be bound by any theory, it is hypothesized that these latter two mechanisms of activity may be accomplished by lower plasma concentrations of paclitaxel than the amount necessary to induce microtubule disruption. Thus, treatment methods, heretofor unknown, using paclitaxel at lower plasma concentrations may be possible to treat diseases or pathologies.

The present invention also comprises compositions and methods of treatment of AIDS-associated Kaposi's sarcoma in patients who have not responded to or who have been intolerant

of previous systemic chemotherapy. Such systemic chemotherapy may include, but is not limited to, treatments involving Doxil® or DaunoXome®. Doxil® is an approved therapy for use in patients who have failed prior chemotherapy, whereas DaunoXome® is not. These drugs are broadly classified as liposomal anthracylines. Thus, the present invention contemplates compositions and methods comprising paclitaxel treatments for patients with AIDS-associated Kaposi's sarcoma who have failed at least one systemic chemotherapy treatment.

An aspect of the present invention is to provide paclitaxel compositions and methods that are commensurate with, and complementary with, antiretroviral therapy treatment for HIV patients according to approved therapies provided by governmental agencies such as the guidelines provided by the Department of Health and Human Services. Examples of such guidelines are the 1997 drafts of the Report of the NIH Panel to Define Principles of Therapy of HIV Infection, and Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Such guidelines are both announced in the Federal Register and are available from the National AIDS Clearinghouse (http://www.cdcnac.org) and from the HIV/AIDS Treatment Information Service (http://www.hivatis.org). Guidelines are also available at http://www.nih.gov/pr/jun'97,niaid-19 htm. Such documents are herein incorporated in their entirety. Final forms of the documents are published in the Center for Disease Control and Prevention Morbidity and Mortality Weekly Report.

The Guidelines recommend starting treatment with three drugs and changing at least two drugs when there are indications that treatment is failing, such as when HIV levels in the blood increase. Treatment with only two drugs, in general, is considered less than optimal. Treatment with only one drug is not recommended. However, monotherapy of zidovudine (AZT) is recommended prophylaxis to prevent HIV transmission to a baby and should be given to relatively healthy HIV-infected pregnant women.

The Guidelines recommend that all patients with AIDS, as defined by the 1993 CDC Classification System, or those with symptomatic HIV infection, should be placed on antiretroviral therapy regardless of viral load. Asymptomatic patients with CD+4 T cell count of less than 500 or with HIV RNA levels greater than 10,000 copies (by bDNA test) or greater than 20,000 copies (by RT-PCR test) should be offered therapy. However, other considerations, such as drug toxicity and willingness of the patient to start therapy and comply, will affect the strength of the recommendation for therapy.

A regimen suggested by the Guidelines is for treatment of HIV infected patients with two nucleoside reverse transcriptase inhibitors and one protease inhibitor to achieve maximum viral suppression. An alternative suggested regimen is to substitute nevirapine for the protease inhibitor. For acute infection with HIV, the combination of two nucleoside inhibitors and one protease inhibitor is recommended. It is also suggested that if antiviral therapy is halted for an extended time, that treatment with all of the antiviral drugs cease, rather than continuing treatment with one or two drugs, to minimize the potential for encouraging resistant viral strains.

There are also suggested considerations for changing treatments in view of a failing regimen. Considerations include distinguishing between drug failure and drug toxicity. Drug toxicity requires the substitution of a different drug for the suspected toxicity causing agent, whereas in drug failure, at least two of the drugs must be changed.

Preferred embodiments of the present invention include the treatment of patients with AIDS-associated Kaposi's sarcoma at dosages of a taxane at 20 mg/m^2 to 200 mg/m^2, more preferably at doses of 50 mg/m^2 to 150 mg/m^2, most preferably 100 mg/m^2, the dose level being dependent on the efficacy and toxicity of paclitaxel on the patient. It is contemplated in the present invention that treatment dosages may change, especially from an initial induction period dosage to a long-term

maintenance period dosage. A preferred embodiment of the method of administration for initial induction period is a dosage of approximately 100 mg/m^2 of a taxane and a dosage of 20 mg/m^2 to 80 mg/m^2, more preferably 25 to 50 mg/m^2.

The infusion schedule for such methods include duration of at least 3 hours every two weeks, for more than at least 10 cycles of treatment As used herein one cycle means one infusion treatment with a taxane, which in a preferred embodiment, one cycle equals a two to four week period.

Administration of taxanes within this range, at doses lower than 100 mg/m^2 is also contemplated within the present invention. Treatments comprising lower than 100 mg/m^2 for patients who cannot tolerate the 100 mg/m^2 dosage level confers successful outcomes for these patients. Additionally, the present invention is not limited by the length of time between the administration of the taxane compositions. The time between cycles, the period of taxane administration may be less than 10 days, or greater than 14 days such as at least 30 days. The length of time between taxane administrations may be dependent on the immune status of the patient or other medical considerations. Such considerations are well known to those skilled in the art and do not provide a limitation to the practice of the present invention.

Compositions included in the present invention include taxanes, preferably paclitaxel or taxotere, most preferably paclitaxel. Such compositions also comprise mixtures of taxanes. In a most preferred embodiment, the present invention comprises compositions and methods of treatment of patients with AIDS-associated Kaposi's sarcoma who undergo intravenous infusion of paclitaxel in a 3 hour infusion rate with a dose of 100 mg/m^2 paclitaxel every 14 days and who are also undergoing antiviral treatment with a viral protease inhibitor. Another preferred embodiment comprises oral paclitaxel compositions and methods of treatment that provide a treatment similar to the intravenous infusion in patients who are undergoing antiviral treatment with a

viral protease inhibitor. Other preferred embodiments comprise compositions and methods of treatment of patients with AIDS-associated Kaposi's sarcoma who undergo intravenous infusion of paclitaxel in a 3 hour infusion rate with a dose of 100 mg/m^2 paclitaxel every 14 days and who have previously failed treatment by systemic chemotherapy. Another preferred embodiment comprises oral paclitaxel compositions and methods of treatment that provide a treatment similar to the intravenous infusion in patients who have previously failed treatment by systemic chemotherapy. Preferred embodiments of the present invention include treatments with paclitaxel, administered in any available form, and may be used for AIDS-associated Kaposi's sarcoma patients who have both failed previous systemic chemotherapy treatments and who are undergoing antiretroviral therapy, such as that recommended by the U.S. Department of Health and Human Services, and therapies that include a protease inhibitor.

As used herein, paclitaxel (USAN generic name) is 5ß, 20-epoxy-1,2α,4,7ß,10ß,13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 12-ester with (2R,3S)-Nbenzoyl-3-phenylisoserine.

The patients to be treated by the present invention include humans with AIDS-associated Kaposi's sarcoma who are undergoing antiviral therapy with viral protease inhibitors and other antiviral agents. The present invention also contemplates treatment of AIDS patients who are undergoing antiviral treatments that are metabolized by the liver and that are also known to effect the pharmacokinetics of concomitantly used drugs. Integrase treatments are also contemplated with the compositions and methods of the present invention. In one embodiment of the present invention, the methods and compositions are useful for patients who have previously undergone liposomal anthracycline treatment for Kaposi's sarcoma wherein such treatment was unsuccessful.

Kaposi's sarcoma (KS) as used herein refers to the Kaposi's sarcoma associated with infection with a virus that causes

AIDS (Acquired Immunodeficiency Disease Syndrome). Prior to the advent of AIDS, Kaposi's sarcoma was described as a rare tumor occurring mainly in elderly men of Mediterranean or Ashkenazi Jewish descent. The KS of these elderly men was characterized by lower extremity skin nodules caused by blood vessel proliferation. AIDS-associated Kaposi's sarcoma has a very different clinical course and patient population. The AIDS-associated Kaposi's sarcoma is an aggressive and widely disseminated neoplasm that can be found in any structure in the body of the person with AIDS. The AIDS-associated Kaposi's sarcoma can be life threatening and highly disabling.

Several cytotoxic treatments have been used to treat the aggressive AIDS-associated Kaposi's sarcoma, including vinca alkaloids, vincristine, platinum, bleomycin and anthracyclines. Combinations of these agents, such as ABV therapy, a combination of doxorubicin (adriamycin), bleomycin and vincristine, have induced responses in as much as 40% of the treated patients. Liposomal DaunoXome® and Doxil® are gaining rapid acceptance for treatment of advanced AIDS-associated Kaposi's sarcoma because the response rates are comparable to ABV but show a better toxicity profile. However, for patients who have failed DaunoXome® or Doxil® and ABV, few therapeutic options remain. The compositions and methods of the present invention have been shown to be safe and effective in such patients.

With most AIDS treatment regimens, the overriding determinants of clinical response and survival are the extent of CD4+ cell destruction and history of opportunistic infection. Alpha interferon has also induced responses, most commonly in patients with CD4+ counts above 150/mm^3, and when used in combination with AZT there is some evidence of synergy. See Fischl, M.A. "Antiviral Therapy in combination with Interferon for AIDS-related Kaposi's Sarcoma," Am. J. Med. 902S. (1991).

The advent of new treatments for the underlying viral infection of patients with AIDS-associated Kaposi's sarcoma

has affected the possible treatments for KS. Several of the new viral therapies, such as viral protease inhibitors, can modify the pharmacokinetics of drugs used to treat AIDS-associated Kaposi's sarcoma. The viral proteases inhibitors are metabolized by the liver and thus, effect the metabolism of many other drugs. For example, paclitaxel is cautioned for use with one viral protease inhibitor, ritonavir, because of the potential large increase in the plasma concentration-time curve of paclitaxel. Other viral treatments may also effect paclitaxel pharmacokinetics and are thus contemplated by the present invention.

In most countries, paclitaxel has been registered for both platinum pretreated ovarian cancer and for anthracycline-resistant breast cancer in a dosage of 175 mg/m^2 administered as a three-hour infusion. Most pharmacokinetic data of paclitaxel have been gathered during phase I clinical trials in which the drug was given as a one-hour infusion daily for five days (15-30 mg/m^2); as a six-hour infusion (15-275 mg/m^2); as a 24-hour infusion (100-390 mg/m^2); or as a 96-hour infusion (120-160 mg/m^2). Evidence from a sensitive assay of the metabolism of paclitaxel indicates that the drug circulates for a prolonged period of time. See Huizing, M.T. and Beijnen, J.H., "Bioanalysis and Clinical Pharmacology of Paclitaxel," Taxane Journal, Vol. II, No. 1 May, 1996.

Early studies indicated a linear pharmacokinetic behavior of paclitaxel with the clearance independent of dose and schedule. Other schedules and doses however, have shown that the pharmacokinetic behavior is non-linear. When paclitaxel is given during a 24-hour infusion there are linear kinetics. When paclitaxel is administered in six hours or less as an intravenous infusion, non-linear pharmacokinetics become apparent. When paclitaxel is administered as a 3-hour infusion at dosages above 135 mg/m^2, the paclitaxel clearance decreases within increasing dose, indicating non-linear saturation pharmacokinetics. This phenomenon appears with the maximal plasma concentration values which increase exponentially with dose. These findings

were thought to be consistent with saturable processes of elimination with paclitaxel, occurring when the plasma concentrations of the drug are above the level of saturation. The occurrence of non-linear pharmacokinetic behavior may have clinically important consequences, as this kinetic behavior may lead to dramatic changes in drug exposure when changing dose and or schedule. See Huizing, M.T. and Beijnen, J.H., "Bioanalysis and Clinical Pharmacology of Paclitaxel," Taxane Journal, Vol. II, No. 1 May, 1996.

Prior to the present invention, there was great uncertainty in the combination of taxane treatments, which are known to be highly sensitive to dose or schedule administration, with viral protease inhibitor treatments, which are known to effect the metabolism of taxanes. Thus prior teachings of use of paclitaxel, or other taxanes, for treatment of AIDS-associated Kaposi's sarcoma provide no teaching or suggestion for the combination of taxanes with viral protease inhibitors for AIDS-associated Kaposi's sarcoma. Paclitaxel has been used to treat KS, but until the present invention, there has been no treatment of KS in patients undergoing viral protease inhibitor treatment. It has been the present inventors surprising discovery that treatment of AIDS-associated Kaposi's sarcoma in patients undergoing AIDS treatment with viral protease inhibitors such as Norvir, with paclitaxel, administered in multiple cycles has provided a safe and effective treatment for AIDS-associated Kaposi's sarcoma. The plasma levels of paclitaxel obtained during and after a 100 mg/m^2 infusion were surprisingly lower than those obtained at doses of 135 mg/m^2, the dose which was the lowest one available from the published literature. Additionally, in two other patients treated with paclitaxel alone, and after two weeks of indinavir therapy, the surprising result was found that the patients did not show an appreciable difference in plasma paclitaxel concentration over time.

The following description teaches the administration of a composition comprising paclitaxel. Use of other taxanes in

place of the paclitaxel is considered part of the present invention. Use of other medical devices such as containers and infusion equipment is also contemplated by the present invention.

Paclitaxel BNP (Baker Norton Pharmaceutical) is generally supplied as a concentrated sterile solution, 6 mg/mL in 5 ampules (30 mg/ampule). Each mL of sterile solution contains 527 mg polyoxyethylated castor oil (Cremophor® EL) and 49.7% (w/v) absolute alcohol BP. The contents of the ampules must be diluted prior to clinical use. The unused portions of any opened ampules should be disposed of using OSHA approved guidelines.

Vials are stored either room temperature (approximately 25° C) or under refrigeration (2-8° C). Each paclitaxel infusion solution should be administered within 24 hours after preparation. Paclitaxel infusion solutions may exhibit a slight haziness directly proportional to the concentration of drug and time elapsed after preparation. When prepared, paclitaxel infusion solutions are stable at ambient temperature (approximately 25° C) and normal lighting conditions for up to 48 hours. Formation of a small number of fibers in the paclitaxel infusion solution (within acceptable limits established by the USP Particulate Matter Test for LVP's) has been observed after preparation of paclitaxel infusion solutions. While particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used. In-line filtration may be necessary and can be accomplished by incorporating a hydrophilic, microporous filter with a pore size no greater than 0.22 microns (IVEX-HP In Line Filter Set-SL, 15", Abbott model #4525 or equivalent) into the fluid pathway distal to the infusion pump.

Paclitaxel must be prepared in nonplasticized solution containers (e.g., glass, polyolefin, or polypropylene) due to leaching of diethylhexylphthlalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing. Paclitaxel must not be administered through PVC intravenous sets. Therefore, polyolefin- or polyethylene-line sets, such as IV

nitroglycerin sets (or equivalent) should be used to connect the container of the paclitaxel infusion solution to the IV pump, a 0.22 micron filter is then attached to the IV set, and then may be directly attached to the patient's central access device. If necessary, a polyolefinline extension set (Polyfin™ - Extension Set, MiniMed technologies, Model #126) can be used to provide additional distance between the IV pump and the patient's central access device.

To practice one embodiment of the invention, the final paclitaxel infusion solution may be prepared by diluting the total paclitaxel dose (i.e., a 3 hour supply) in 250 or 500 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP in either a glass, polyolefin or polypropylene container. The paclitaxel infusion solution will be infused over 3 hours through any methods known to those skilled in the art. Should a pump be used, a polyolefin- or polyethylene-line set should be used to connect the bag/bottle to the IV pump, followed by the in-line filter. The patient may or may not have a central access device which can be used for the infusion.

An embodiment of the present invention comprises administration of a paclitaxel infusion solution as a 3 hour continuous intravenous infusion. The paclitaxel infusion solution can be delivered using any methods known in the art, with cycles repeated every 14 days. Alternatively, oral administration of taxanes that provide pharmacokinetic benefit, such as plasma levels of paclitaxel in therapeutic ranges, could be administered without requiring the patient to have a venous access.

Because of the possibility of anaphylactic reactions, a physician should be available during the first 30 minutes of each infusion, and intravenous epinephrine, hydrocortisone, and diphenhydramine should also be kept available.

A preferred embodiment of the present invention is a method of treatment of patients with AIDS-associated Kaposi's sarcoma who have had disease progression after prior treatment with liposomal anthracyclines. A most preferred embodiment of

the present invention is a method of treatment of humans with AIDS-associated Kaposi's sarcoma who have refractory KS and who are concurrently undergoing antiviral therapy such as treatment with viral protease inhibitors.

This invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims.

Example I

Treatment of AIDS-associated Kaposi's sarcoma consisted of a 3-hour infusion of paclitaxel at 100 mg/m^2 administered every 14 days for the first 10 cycles. The paclitaxel, 5ß, 20-epoxy-1,2α,4,7ß,10ß,13a-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 12-ester with (2R,3S)-Nbenzoyl-3-phenylisoserine, was supplied as a concentrated sterile solution, 6 mg/mL in 5 mL ampules (30 mg/ampule). Each mL of sterile solution contains 527 mg polyoxyethylated castor oil (Cremophore® EL) and 49.7% (w/v) absolute alcohol BP. The contents of the vials must be diluted prior to clinical use. The unused portions of any opened vials should be disposed of using OSHA approved guidelines, and/or institutional policy. Vials should be stored either at room temperature (approximately 25° C) or under refrigeration (2-8° C). Each bag/bottle should be administered within 24 hours after preparation.

Solutions of paclitaxel may exhibit a slight haziness directly proportional to the concentration of drug and time elapsed after preparation. Solutions of paclitaxel for infusion (0.3

- 1.2 mg/mL) are stable at ambient temperature (approximately 25°C) and normal lighting conditions for up to 48 hours.

All of the patients treated had AIDS-associated Kaposi's sarcoma with measurable disease and had received at least one prior chemotherapy regimen. The patients had microscopically confirmed diagnosis of KS associated with HIV infection for which systemic therapy is medically indicated by the presence of at least one of the following: greater than 25 mucocutaneous (mouth or skin) lesions; visceral involvement; symptomatic lymphedema (pain); by physical exam or measurable disease by X-ray, CT or MRI; and had at least one systemic chemotherapy regimen which failed to maintain significant benefit. Intralesional chemotherapy regimens was not considered as prior chemotherapy.

All patients underwent a 3 hour paclitaxel infusion of 100 mg/m^2 every two weeks. The following medications were administered prior to infusion to minimize the risk of hypersensitivity reactions: Dexamethasone 10-20 mg p.o. at 12 hours and again at 6 hours prior to beginning paclitaxel infusion. Dexamethasone 20 mg IV, 60 min. prior to paclitaxel infusion, may be substituted for the p.o. dose. The intravenous dose was reduced to 8-10 mg in subsequent cycles if no hypersensitivity reaction was noted in cycles one and two; cimetidine 300 mg or ranitidine 50 mg IV (intravenously) and diphenhydramine 50 mg IV (or p.o.) one hour before the beginning of paclitaxel infusion.

All tumor response classifications were made by comparing current lesion characteristics (i.e., size, number appearance and sites of involvement) to the patients' baseline tumor evaluations. If the patient had numerous cutaneous lesions, 5 discrete marker lesions were followed with bidimensional tumor measurements. Total body cutaneous lesions (up to 50) were counted every cycle with an indication as to the number of flat and raised lesions.

Patient response was measured as follows.

Complete response (CR): the absence of any detectable disease, including tumor-associated edema, lasting at least 4 weeks.

Partial Response (PR) No new lesions (skin or oral), no new visceral sites of involvement or the appearance or worsening of tumor-associated edema or effusions and a 50% or greater decrease in the number of all previously existing lesions, (the decrease in the count must last at least 4 weeks); or a 50% decrease in the sum of the products of the diameters of all measurable visceral lesions lasting for at least 4 weeks; or complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all previously nodular or plaque-like lesions become macules); or 50% decrease in the sum of the products of the largest perpendicular diameters of the five marker lesions.

Stable disease (SD): patients who do not qualify for response nor progressive disease.

Progressive disease (PD): new visceral sites of involvement or progression of visceral disease (i.e., increase in lesions or effusion on chest x-ray, increase in size or number of gastrointestinal lesions by endoscopy); or the development of new or increasing tumor-associated edema lasting at least one week and which interferes with the patient's normal activities; or a 25% increase in the number of lesions; or a change in the character of 25% or more of all previously "flat" lesions to "raised" (i.e., 25% of all previously macular lesions become nodular or plaque-like); or a 25% increase in the sum of the products of the largest perpendicular diameters of the marker lesions.

Paclitaxel was given as a 3-hour infusion every 14 days for the first 10 cycles. After 10 cycles, the interval between cycles was 14-28 days. The dose of 100 mg/m^2 was diluted in 5% dextrose for injection, USP, or 0.9% sodium chloride for injection, USP to a concentration of 0.3 to 1.2 mg/mL. Paclitaxel was administered through a free-flowing intravenous line via a pump using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) used to infuse

parenteral nitroglycerin. No other agent was infused concomitantly through the line used to administer paclitaxel.

Paclitaxel was administered through an in-line filter with a microporous membrane not greater than 0.22 microns (e.g. IVEX 2). Solutions with excessive particulate formulation were discarded. After dilution, each bag/bottle was administered within 24 hours. A central line was not required for patients receiving a 3-hour infusion.

Eighty-nine patients were treated with paclitaxel for AIDS-associated Kaposi's sarcoma. All patients had advanced KS and all had been previously treated with systemic chemotherapy. Sixty of the 89 patients had starting CD4 counts <200 while 49 of these patients had CD4 counts <50. Twenty-seven patients had disfiguring facial lesions, 37 had lymphedema and 28 had visceral disease involving the lungs and/or the gastrointestinal tract.

All of the patients had previously undergone at least one systemic chemotherapy treatment for KS. Forty-three patients had previously received either vincristine or vinblastine (V); bleomycin and vincristine (BV) or Adriamycin®, bleomycin and vincristine (ABV). Forty-one patients had previously received liposomal DaunoXome®. Twenty-seven patients had previously received Doxil®. A total of 51 of the patients had received one or both of the systemic liposomal anthracycline drugs which had been unsuccessful in treating the AIDS-associated Kaposi's sarcoma. Of these 51 patients, 33 patients responded to treatment with paclitaxel, for a 65% response rate.

Among the 89 patients, there was an overall 52% response rate. Patients previously receiving V, BV, or ABV had a 65% response rate (28/43) while patients who previously received DaunoXome® had a 51% (21/41) response rate. Patients who had previously received Doxil® had a 41% (11/27) response rate.

Of these 89 patients, two patients had a complete response and 44 had partial responses (PR). A majority of the patients were taking viral protease inhibitors at some time during

the paclitaxel treatment. The 89 patients were treated with paclitaxel with from one to 27 cycles of treatment (median of 8 cycles). Thirty-four patients have been treated with more than 10 cycles of treatment. Such therapy represents maintenance treatment beyond the first 10 cycles of induction therapy.

Pharmacokinetic studies were performed in 9 of the patients during cycle 6 to 11. Peak concentration, area under the plasma concentration curve, volume of distribution and body clearance are presented in the following table. A comparison is made to data obtained from 135 mg/m^2 and 175 mg/m^2 treatment in patients with solid tumors.

Table I: Pharmacokinetic comparisons

Tumor Type	Dose (mg/m^2)	N	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	CL (L/hr/m^2)	V_{dss} (L/m^2)	t1/2 (hr)
AIDS-KS	100	9	1118	3551	27.4	402	24.8
			(26.8)	(25.1)	(25.2)	(37.7)	(25.0)
Lung cancer	135	3	5687	14446	10.8	14.4	1.6
			(47.6)	(61.4)	(53.8)	(38.8)	(29.2)
Lung cancer	175	6	7852	22457	8.7*	22.1*	8.8*
			(44)	(43.6)	(54.1)	(51.1)	(79.0)
Breast/ Ovarian cancer	175	8	4214	12604	20.4	136.1	8.9
			(46.2)	(52.2)	(84.9)	(118.0)	(46.1)

Example II

Treatment of AIDS-associated Kaposi's sarcoma consisted of a 3-hour infusion of paclitaxel at 100 mg/m^2 administered every 14 days as in the manner described in Example 1. This patient was a 32-year-old white male who was diagnosed HIV-positive in July 1993 and has had Kaposi's

sarcoma since April 1994. KS involvement included the skin, mouth, and inguinal nodes. By staging, he was a poor risk for tumor and systemic involvement and a good risk for immune status. Previous chemotherapy prior to entering the protocol included VP16, vincristine-vinblastine, and alpha-interferon, to which his best response was progressive disease. The patient was treated with anti-retroviral therapy starting at cycle 2 which consisted of the protease inhibitor indinavir and two reverse transcriptase inhibitors, zidovudine and lamivudine. Triple anti-retroviral drug therapy was continued throughout his treatment, which continued to cycle 19, although indinavir was switched to ritonavir after cycle 11. The patient tolerated treatment well, with only two episodes of adverse events of grade 3 or greater. One episode was a grade 3 fever and the other episode was a grade 3 heartburn. The fever was not considered by the investigator to be attributable to paclitaxel, however the heartburn was.

This patient showed a partial response to paclitaxel treatment. The Karnofsky performance scale showed an improvement from 70 at baseline to 80 during the study and the Symptom Distress Scale showed an improvement from 38 at baseline to 32 at cycle 10. Since the patient had greater than 50 lesions, 28 lesions on the arms and back were followed, of which a maximum of 21 resolved during treatment and only three remained raised. Also, at baseline the patient had extensive scrotal edema along with darkened lesions and edema of the right leg. By cycle 4, the scrotal edema markedly decreased and this improvement persisted through cycle 19. A marked decrease in the circumference of the right upper leg occurred during treatment from about 65 cm at baseline to <58 cm through cycle 19. The upper left leg also showed a decrease from about 60 cm at baseline to about 57 cm through cycle 19.

Example III

Initial treatment of AIDS-associated Kaposi's sarcoma consisted of a 3-hour infusion of paclitaxel at 100 mg/m^2 administered every 14 days as in the manner described in Example 1, followed by treatment at 75 mg/m^2. This patient was a 33-year-old black male who was diagnosed HIV-positive in December 1994 and has had Kaposi's sarcoma since February 1995. KS involvement included the skin, face, mouth, and GI tract. By staging, he was a poor risk defined by tumor and immune status and a good risk defined by systemic involvement. Previous chemotherapy prior to entering the protocol included DaunoXome® to which he showed stable disease but had toxicity, and Adriamycin®, bleomycin and vincristine, (ABV) to which he responded partially, but subsequently failed. The patient was on antiretroviral therapy at the time he entered the protocol which consisted of the protease inhibitor indinavir and two reverse transcriptase inhibitors, stavudine and lamivudine. He continued on these medications throughout his treatment which went to cycle 17. Because the patient experienced a grade 4 neutropenia after the first cycle of paclitaxel, his dose was reduced to 75 mg/m^2 and he was treated with this dose through 17 cycles of treatment. The patient also experienced a grade 3 urinary tract infection and a grade 3 infection of a scrotal ulcer which were considered by the investigator to be due to paclitaxel treatment. He also had grade 3 and grade 4 increased alkaline phosphatase and grade 3 pneumonia which were not felt to be attributable to paclitaxel.

During treatment with the reduced dose of paclitaxel (75 mg/m^2) after the first cycle of treatment, this patient showed a partial response to paclitaxel. The Karnofsky performance score improved from 60 at baseline to 90 at cycle 10 and the Symptom Distress Scale score improved from 35 at baseline to 18 at cycle 10. Since the patient had greater than 50 lesions, eight lesions on the left forearm were followed, of which two cleared and four flattened. The patient had extensive facial lesions and

extensive facial edema. A marked decrease in edema and the prominence of facial lesions was seen by cycle 7.

Example IV

Treatment of AIDS-associated Kaposi's sarcoma consisted of a 3-hour infusion of paclitaxel at 100 mg/m^2 administered every 14 days as in the manner described in Example 1. This patient was a 41 year-old black male who was diagnosed HIV-positive in 1990 and had Kaposi's sarcoma since May 1996. KS involvement included the skin, face, and inguinal nodes, with equivocal involvement of the mouth and lung. By staging, he was a poor risk for tumor and immune and a good risk for systemic involvement. Previous chemotherapy prior to entering this protocol was DaunoXome®, to which his best response was progressive disease. When the patient entered the protocol, he was on antiretroviral therapy, which consisted of the protease inhibitors saquinavir and ritonavir and three reverse transcriptase inhibitors, didanosine, stavudine and lamivudine. He continued on these medications throughout his treatment which has gone to cycle 10. The patient tolerated treatment with paclitaxel well with the only serious adverse events experienced being a grade 3 and grade 4 neutropenia which the investigator attributed to paclitaxel.

The patient had a best response to paclitaxel of stable disease through 10 cycles of treatment. His Karnofsky performance score showed a decrease from 90 at baseline to 80 during cycles 3-10, whereas the Symptom Distress Scale, measured at baseline and cycle 4 showed no change. Since the patient had greater than 50 lesions, 22 lesions on his face and upper left thigh were examined, of which one flattened and none cleared. At baseline, numerous lesions were apparent on both legs and the right leg was edematous, with a larger size than the left and marked ankle swelling. The left leg remained larger than the right throughout treatment, although it had appeared to

decrease in size by cycle 4. The lesions appeared less prominent as a result of treatment. Measurement of the circumference of the lower legs showed no change from baseline in either leg (both 30 cm). However, the right upper leg showed a decrease from 59 cm to 57 cm during the study and the left leg a small decrease from 52.8 cm to 51.5 cm.

Example V

Treatment of AIDS-associated Kaposi's sarcoma consisted of a 3-hour infusion of paclitaxel at 100 mg/m^2 administered every 14 days as in the manner described in Example 1. This patient was a 41 year old white male who was HIV-positive since 1985 and has had Kaposi's sarcoma since March 1995. He had pulmonary and skin involvement of KS lesions. By staging, he was a poor risk by tumor, immune and systemic involvement. Previous chemotherapy prior to entering this protocol included both liposomal daunorubicin ([DaunoXome®) to which his best response was a partial response and liposomal doxorubicin (Doxil®) to which his best response was tumor progression. Upon beginning treatment with paclitaxel, he had a partial response beginning at cycle 4. He had significant improvement in his pulmonary KS which was seen as early as cycle 4, with significant improvement persisting out to cycle 19. His breathing, cough and mobility scores improved with paclitaxel treatment. Of note, the patient was on oxygen prior to treatment with paclitaxel, but was able to discontinue this after starting treatment with paclitaxel.

Example VI

Treatment of AIDS-associated Kaposi's sarcoma consisted of a 3-hour infusion of paclitaxel at 100 mg/m^2 administered every 14 days as in the manner described in

Example I was begun with the following patients but due to medical considerations, their schedules were altered as described.

Patient #687 had his dose of paclitaxel reduced to 75 mg/m^2 following the second cycle because of grade 3 hyperbilirubinemia. He continued on this reduced dose from cycles 2 through 7. The patient had a partial response beginning at cycle 6.

Patient #688 had his dose of paclitaxel reduced to 75 mg/m^2 following the fourth cycle after the patient experienced grade 3 diarrhea. He continued on this reduced dose from cycles 5 through 9. The patient had a partial response beginning at cycle 6.

Patient # 692 had his dose of paclitaxel reduced to 75 mg/m^2 following the first cycle because of grade 4 neutropenia. He continued on this reduced dose from cycles 2 through 11. The patient had a best response of stable disease.

Patient #630 had his dose of paclitaxel reduced to 75 mg/m^2 following the 12th cycle after the patient experienced grade 4 neutropenia. He continued on this reduced dose from cycles 13 through 27. The patient had a partial response which persists out to cycle 27, at the reduced dose of paclitaxel.

Example VII

Treatment of AIDS-associated Kaposi's sarcoma consisted of a 3-hour infusion of paclitaxel at 100 mg/m^2 administered every 14 days as in the manner described in Example I was begun with the following patient but due to medical considerations, his schedule was altered as described.

Patient # 637 had the interval of time between cycles increased to between 15-28 days (generally 21-28 days) after his 10th cycle. The patient has received 17 cycles of treatment. Despite this increased interval between treatments (giving a dose intensity of 25-33 mg/m^2 per week) the patient had a partial response maintained between cycles 11 and 17.

Table III shows the antiretroviral medications used by patients in the study detailed in Examples I-VIII. Patients may have received more than one of each class at any time prior to or during study.

Table II: Usage of Antiretroviral Medications

	Number (%) of Patients[1] (N = 89)					
	Started Prior to Study		Started During first 10 cycles		Treatment Date Unknown	
	N	(%)	N	(%)	N	(%)
Protease Inhibitors	33	(37.1)	35	(39.3)	2	(2.2)
Indinavir	21	(23.6)	21	(23.6)	2	(2.2)
Nelfinavir	0	(0.0)	6	(6.7)	0	(0.0)
Ritonavir	3	(3.4)	6	(6.7)	0	(0.0)
Saquinavir	11	(12.4)	8	(9.0)	0	(0.0)
Reverse Transcriptase Inhibitors	59	(66.3)	40	(44.9)	6	(6.7)
Didanosine	5	(5.6)	4	(4.5)	0	(0.0)
Lamivudine	43	(48.3)	18	(20.2)	5	(5.6)
Nevirapine	1	(1.1)	4	(4.5)	0	(0.0)
Stavudine	31	(34.8)	21	(23.6)	2	(2.2)
Zalcitabine	2	(2.2)	1	(1.1)	0	(0.0)
Zidovudine	24	(27.0)	8	(9.0)	2	(2.2)

Patients may have received more than one of each class at any time prior to or during study.

[1]Does not add across columns.

Table III: Best Response By Use of Protease Inhibitors (Evaluable Patients N=77)

		Best Response in First 10 Cycles				
	Total No. of Patients	Success (CR or PR) # (%)	Complete (CR) # (%)	Partial (PR) # (%)	Stable (S) # (%)	Progression (P) # (%)
No Protease Inhibitors Used During Study or Prior to Study	24	19 (79.2)	2 (8.3)	17 (70.8)	4 (16.7)	1 (4.2)
Protease Inhibitors Used Prior to or During Study	53	27 (50.9)	0 (0.0)	27 (50.9)	26 (49.1)	0 (0.0)

Table IV: Tumor Response to Paclitaxel by Previous Systemic Chemotherapy

Treatment	No. of Patients N	**Best Response to Paclitaxel in First 10 Cycles**		
		Success N (%)	Complete N (%)	Partial N (%)
Previous Chemotherapeutic Regimen				
ABV	43	28 (65%)	2 (5%))	26 (60%)
DaunoXome	41	21 (51%)	1 (2%)	20 (49%)
Doxil	27	11 (41%)	0 (0%)	11 (41%)
Other	13	12 (92%)	0 (0%)	12 (92%)
Number of Previous Chemotherapy Treatments				
1 Prior	45	24 (53%)	1 (2%)	23 (51%)
2 Prior	25	17 (68%)	1 (4%)	16 (64%)
> 2 Prior	7	5 (71%)	0 (0%)	5 (71%)

Example VIII

Pharmacokinetic Studies

Patients were enrolled in a clinical study of paclitaxel in AIDS-KS as described in Example I. During one cycle of paclitaxel administration, ranging from cycle 6 to 11 of therapy, patients who volunteered to participate in this study, remained at the clinic for serial plasma samplings. Relative to the 3-hr paclitaxel infusion, 7 mL of blood were obtained using a heparinized Vacutainer® tube for the determination of plasma paclitaxel concentrations at: 0 (pre-infusion), 0.5, 1, 2, 2.5 hr during infusion, 0 (end of infusion), 0.08 (5 minutes), 0.25 (15 minutes), 0.5 (30 minutes), 1, 1.5, 2, 3, 6, 8, 10, 18, 24, 30, and 48 hr post infusion. Each blood sample was centrifuged at 3500 rpm for 10 minutes. The separated plasma was transferred into labeled plastic vials (polypropylene) and then stored at -20°C until assayed.

Plasma concentrations of paclitaxel were determined using a validated LC/MS-MS method. Acetonitrile was added to a 0.8 mL plasma sample to precipitate plasma proteins. After centrifugation, the acetonitrile layer was evaporated to dryness. An aliquot of the reconstituted extract was injected onto a SCIEX AP III plus LC/MS-MS with a HPLC column. The lower limit of quantitation of paclitaxel was 50 pg/mL. Plasma paclitaxel levels were subject to a noncompartmental analysis.

The nine patients from whom this data was obtained were HIV-positive males with advanced AIDS-associated Kaposi's sarcoma (AIDS-KS). The patients (8 white, 1 black) who participated in this pharmacokinetics study had a mean age of 36.3 years (range: 27.7 to 48.5), mean weight of 154.5 kg (range 116 to 180), and mean height of 67.9 in. (range 64 to 72). All patients, with the exception of Patient No. 651, were taking reverse transcriptase nucleoside analogs for their HIV disease. The mean CD4 count at baseline in these patients was 210.8 cells/mm^3 (range: 17 to 640).

Pharmacokinetics: The mean (CV) values for various pharmacokinetic parameters are shown in Table VI.

Table V

C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	CL ($L/hr/m^2$)	$V_{d\beta}$ (L/m^2)	V_{dss} (L/m^2)	t1/2 (hr)
1118	3551	3868	27.4*	980*	402*	24.8*
(26.8)	(25.1)	(27.1)	(25.2)	(33.7)	(37.7)	(25.0)

* n= 8

The pharmacokinetic evaluations occurred during cycles 6 to 11, but there was no relationship between the number of cycles of treatment the patients received and the pharmacokinetic values obtained.

It is noteworthy that the CV for each of these parameters is lower than has been reported for higher doses of paclitaxel given over 3 hr. This suggests that lower doses may exhibit less intersubject variability compared to higher doses.

Although this was not a formal drug-drug interaction study, patients also received numerous agents to treat the underlying HIV infection and intercurrent illnesses. AIDS-KS patients typically receive concomitant antifungal agents, so the pharmacokinetics of paclitaxel were compared in the six patients receiving these concomitant imidazole antifungals and the three patients who were not. There were no differences between these groups. Similarly, comparison of the pharmacokinetics in five patients receiving concomitant indinavir, a protease inhibitor, with those in four patients not receiving this agent showed no significant differences. The mean percent changes in pharmacokinetic values of paclitaxel after 2 weeks of indinavir (800 mg tid) are noted in the following table.

Table VI

Mean Change				
Cmax	AUC_{last}	AUC_{∞}	CL	$Vd\beta$
-16	+19	+26	-15	-2

A number of analyses were done to determine whether demographic or economical status influenced the pharmacokinetic samples obtained. There were no significant relationships between the patient's age and various pharmacokinetic parameters:
[C_{max} (r^2= 0.26), AUC_{last} (r^2 = 0.14), CL (r^2 = 0.11), and Vdss (r^2 = 0.14)].

From an examination of the few patients with moderate elevations of liver function tests, it was concluded that impaired hepatic function may be associated with a modest reduction in the elimination rate of paclitaxel from the systemic circulation.

Previous studies suggested that drug levels maintained above certain levels were associated with a higher incidence of decreases in white blood cell (WBC) and absolute neutrophil counts (ANC). No correlation could be determined between the datum of time paclitaxel levels were above 0.1 or 0.05 μM and changes in WBC and ANC. Five patients had Grade 3 non-hematological toxicities [alopecia (N =3), heartburn (N = 1), and elevated ALT (N = 1)] while participating in this study, although both reports of alopecia occurred prior to the pharmacokinetic study day. There were no appreciable differences in AUC values from patients who developed these adverse events (3650 ng·hr/mL) compared to those who did not (3426 ng·hr/mLng·hr/mL).

There was no apparent difference in the pharmacokinetics of the five patients who were partial responders to paclitaxel administration and the four who were not at the time of the pharmacokinetics study. Three of the remaining patients went on to become partial responders during the study.

The results of this study demonstrate that the exposure to paclitaxel after 100 mg/m^2 dose administered over 3 hours is considerably less than has been reported with conventional doses of 135 mg/m^2 and higher given over this same interval in cancer patients with solid tumors. Body clearance and

volume of distribution of paclitaxel were about 2 to 6 times higher with this lower dose of paclitaxel compared to the previously studied higher doses. As with the higher doses, the pharmacokinetics of paclitaxel appear to be nonlinear. Interpatient variability is lower at this dose than noted in previous studies.

No significant drug-drug or drug level and efficacy or toxicity interactions were noted.

It should be understood, of course, that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the invention as set forth in the appended claims.

What is claimed is:

1. A method for treatment of AIDS associated Kaposi's sarcoma comprising, concomitantly administering an effective dose of a taxane with one or more protease inhibitors to a human.

2. The method of Claim 1, further comprising concomitantly administering one or more reverse transcriptase inhibitors.

3. The method of Claim 1, wherein the dose of taxane is 30 to 200 mg/m^2 every 2 weeks.

4. The method of Claim 1, wherein the dose of taxane is 50 to 155 mg/m^2 every 2 weeks.

5. The method of Claim 1, wherein the dose of taxane is 100 mg/m^2 every 2 weeks.

6. The method of Claim 1, wherein the human has failed therapy with liposomal anthracyclines.

7. The method of Claim 1, wherein the human has failed therapy with liposomal doxorubicin.

8. The method of Claim 1, wherein the human has failed therapy with combinations of adriamycin, bleomycin or vincristine.

9. The method of Claim 1, wherein the human has failed therapy with liposomal anthracyclines and combinations of adriamycin, bleomycin or vincristine.

10. The method of Claim 1, wherein the human has failed two or more prior cytotoxic chemotherapies.

11. The method of Claim 1, wherein the human receives an induction therapy of about 10 weeks.

12. A method of maintenance therapy for Kaposi's sarcoma patients who have responded to induction therapy of about 10 weeks comprising administering an effective dose of a taxane every 8 to 30 days.

13. The method of Claim 12, wherein the dose of taxane is between 50 to 100 mg/m^2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/06221

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/20
US CL :514/449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Database CANCERLIT on STN, Accession No. 1998642829, DULCHIN K. et al., "Pharmacokinetics of low-dose Paxene (paclitaxel) in patients with refractory or relapsed AIDS-related Kaposi's sarcoma" (Meeting abstract), University of Southern California School of Medicine, Los Angeles, CA., Proc. Annu Meet Am Soc Clin Oncol. 1997, Vol. 16, pp. A829.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
17 JUNE 1998	29 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DWAYNE C. JONES Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/06221

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

CA, EMBASE, MEDLINE, BIOSIS, CANCERLIT, USPATFULL, TOXLIT, TOXLINE, WPIDS, AIDSLINE search terms: taxane# or taxol# or paclitaxel#, aids, kaposi's sarcoma or KS or kaposi?, protease(3a)inhibitor# or norvir or retonavir or indinavir or nelfinavir